

## WHAT IS CLAIMED IS:

1. A GHRH analogue, a functional derivative of said analogue, or a pharmaceutically acceptable salt thereof comprising formula X: Tyr-A2-Asp-Ala-Ile-Phe-Thr-A8-A9-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-A21-A22-Leu-Gln - Asp -Ile- Met - Ser -Arg-A30- NH<sub>2</sub>, wherein  
A2 is Ala or D-Ala;  
A8 is Asn, D-Asn or Ala;  
A9 is Ser or Ala;  
10 A10 is Tyr or D-Tyr;  
A15 is Gly, Ala or D-Ala;  
A21 is Lys or D-Lys;  
A22 is Leu, D-Leu, Lys or Ala; and  
A30 is a bond or any amino acid sequence of 1 up to 15 residues;  
15 said analogue, functional derivative of said analogue or salt thereof having an *in vitro* potency index substantially higher than the *in vitro* potency index of a naturally occurring GHRH.
2. The GHRH analogue, functional derivative or salt thereof of claim 1, wherein said analogue is selected from the group consisting of, and wherein:  
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  - A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys; A9, A10, A21 and A30 are as defined in claim 1;
  - A2 is D-Ala, A10 is D-Tyr, and A22 is Lys; A8, A9, A15, A21 and A30 are as defined in claim 1; and
  - A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys; A8, A9, A21 and  
25 A30 are as defined in claim 1.
3. The GHRH analogue, functional derivative or salt thereof of claim 1, wherein said analogue is selected from the group consisting of, and wherein:

A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys; A9, A10, A21 and A30 are as defined in claim 1.

4. The GHRH analogue, functional derivative or salt thereof of claim 1, wherein said analogue is selected from the group consisting of, and wherein:

5 A2 is D-Ala, A10 is D-Tyr, and A22 is Lys; A8, A9, A15, A21 and A30 are as defined in claim 1.

5. The GHRH analogue, functional derivative or salt thereof of claim 1, wherein said analogue is selected from the group consisting of, and wherein:

10 A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys; A8, A9, A21 and A30 are as defined in claim 1.

6. A GHRH analogue according to any one of claims 1 to 5, wherein the *in vitro* potency index is at least 500-fold higher than the *in vitro* potency index of a naturally occurring GHRH.

15 7. The GHRH analogue of claim 6, wherein the *in vitro* potency index is at least 1500-fold higher than the *in vitro* potency index of a naturally occurring GHRH.

8. The GHRH analogue of claim 7, wherein the *in vitro* potency index is at least 2500-fold higher than the *in vitro* potency index of a naturally occurring GHRH.

9. A pharmaceutical composition comprising:

- 20 - an effective amount of a GHRH analogue, a functional derivative of said analogue or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 8; and  
- a pharmaceutically acceptable carrier.

25 10. Use of an effective amount of a GHRH analogue, a functional derivative of said analogue or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 8, or of a pharmaceutical composition, as defined in claim 9, for specific stimulation of *in vivo* GH release.

11. Use of an effective amount of a GHRH analogue, a functional derivative of said analogue or a pharmaceutically acceptable salt thereof, as defined in any one of

claims 1 to 8, or of a pharmaceutical composition as defined in claim 9, for preparation of a drug in the treatment of GH deficiency-related conditions.

12. The use according to claim 11, wherein said conditions are selected from the group consisting of: hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union bone-fracture, acute/chronic debilitating illness or infection, wound healing, reduction of the incidence of post-surgical problems, lactation failure, infertility in women, cachexia in cancer patients, anabolic and/or catabolic problems, T-cell immunodeficiencies, neurodegenerative conditions, GHRH receptor-dependent tumors, aging, sleep disorders, muscle wasting diseases such as in sarcopenic patients, frail elderlies, HIV patients and cancer patients having radiotherapy and chemotherapy-related side effects.

13. The use according to claim 12, wherein said muscle wasting diseases are selected from the group consisting of: sarcopenia, frailty in elderlies, HIV and cancer.

14. A method for initiating GHRH-induced biological actions in a mammal, said method comprising the step of:

- administering, to said mammal, an effective amount of a GHRH analogue, a functional derivative of said analogue or a pharmaceutically acceptable salt thereof, as defined in any one of claims 1 to 8, or of a pharmaceutical composition as defined in claim 9.

15. The method of claim 14, wherein said GHRH- induced biological actions are selected from the group comprising: regulation of sleep disorders, regulation of food-intake disorders and increase in protein synthesis.

16. The method according to claim 15, wherein the increase in protein synthesis results in an increase in muscle mass or an increase in milk production.

17. A GHRH analogue or a pharmaceutically acceptable salt thereof able to stimulate secretion or synthesis of growth hormone in a mammal, said GHRH analog or pharmaceutically acceptable salt having an *in vitro* potency index substantially higher than the *in vitro* potency index of a native hGHRH1-29 and having formula Tyr- D-Ala<sup>2</sup>-Asp-Ala-Ile-Phe-Thr-Asn- Ser-D-Tyr<sup>10</sup>-Arg-Lys-Val-Leu- D-Ala<sup>15</sup>-Gln-Leu-Ser-Ala-Arg-Lys-Lys<sup>22</sup>-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH<sub>2</sub>, wherein A30 is a bond or any amino acid sequence of 1 up to 15 residues.
18. A GHRH analogue according to claim 17, wherein the *in vitro* potency index is at least 500-fold higher than the *in vitro* potency index of a native hGHRH1-29.
19. The GHRH analogue of claim 18, wherein the *in vitro* potency index is at least 1500-fold higher than the *in vitro* potency index of a native hGHRH1-29.
20. The GHRH analogue of claim 19, wherein the *in vitro* potency index is at least 2500-fold higher than the *in vitro* potency index of a native hGHRH1-29.
21. The GHRH analogue of claim 17, wherein said GHRH analogue has the formula Tyr- D-Ala<sup>2</sup>-Asp-Ala-Ile-Phe-Thr-Asn- Ser-D-Tyr<sup>10</sup>-Arg-Lys-Val-Leu- D-Ala<sup>15</sup>-Gln-Leu-Ser-Ala-Arg-Lys-Lys<sup>22</sup>-Leu-Gln-Asp-Ile-Met-Ser-Arg -NH<sub>2</sub>.
22. A pharmaceutical composition, comprising:
- a) an effective amount of a GHRH analogue or a pharmaceutically acceptable salt thereof comprising formula X: Tyr-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH<sub>2</sub>, wherein  
A2 is Ala or D-Ala;  
A8 is Asn, D-Asn or Ala;  
A10 is Tyr or D-Tyr;  
A15 is Gly, Ala or D-Ala;  
A22 is Leu, D-Leu, Lys or Ala; and  
A30 is a bond or any amino acid sequence of 1 up to 15 residues and wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29; and;
  - b) a pharmaceutically acceptable carrier.

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23. The pharmaceutical composition of claim 22, wherein said GHRH analogue or salt thereof is selected from the group consisting of, and wherein:

- A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys;
- A2 is D-Ala, A10 is D-Tyr, and A22 is Lys and;
- A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys.

24. The pharmaceutical composition of claim 23, wherein A2 is D-Ala, A8 is Asn, A10 is D-Tyr, A15 is D-Ala, A22 is Lys and A30 is a bond.

25. A pharmaceutical composition, comprising:

- a) an effective amount of a GHRH analogue or a pharmaceutically acceptable salt thereof of formula X: Tyr-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH<sub>2</sub>, wherein

A2 is Ala or D-Ala;

A8 is Asn, D-Asn or Ala;

A10 is Tyr or D-Tyr;

A15 is Gly, Ala or D-Ala;

A22 is Leu, D-Leu, Lys or Ala; and

A30 is a bond or any amino acid sequence of 1 up to 15 residues and wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29; and;

- b) a pharmaceutically acceptable carrier.

26. The pharmaceutical composition of claim 25, wherein said GHRH analogue or salt thereof is selected from the group consisting of, and wherein:

- A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys;
- A2 is D-Ala, A10 is D-Tyr, and A22 is Lys and;
- A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys.

27. The pharmaceutical composition of claim 26, wherein A2 is D-Ala, A8 is Asn, A10 is D-Tyr, A15 is D-Ala, A22 is Lys and A30 is a bond.

28. A pharmaceutical composition for stimulating secretion or synthesis of growth hormone in a mammal in need thereof, the pharmaceutical composition comprising:

- a) an effective amount of a GHRH analogue or a pharmaceutically acceptable salt thereof comprising formula X: Tyr-A2-Asp-Ala-Ile-Phe-

Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH<sub>2</sub>, wherein

A2 is Ala or D-Ala;

A8 is Asn, D-Asn or Ala;

5 A10 is Tyr or D-Tyr;

A15 is Gly, Ala or D-Ala;

A22 is Leu, D-Leu, Lys or Ala; and

10 A30 is a bond or any amino acid sequence of 1 up to 15 residues and wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29, and;

b) a pharmaceutically acceptable carrier.

29. The pharmaceutical composition of claim 28, wherein said GHRH analogue or salt thereof is selected from the group consisting of, and wherein:

15 - A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys;

- A2 is D-Ala, A10 is D-Tyr, and A22 is Lys and;

-A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys.

30. The pharmaceutical composition of claim 29, wherein A2 is D-Ala, A8 is Asn, 20 A10 is D-Tyr, A15 is D-Ala, A22 is Lys and A30 is a bond.

31. The use of a GHRH analogue, or a pharmaceutically acceptable salt thereof in the preparation of a pharmaceutical composition for stimulating secretion or synthesis of growth hormone in a mammal in need thereof, said GHRH analog or 25 pharmaceutically acceptable salt comprising formula X: Tyr-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH<sub>2</sub>, wherein

A2 is Ala or D-Ala;

A8 is Asn, D-Asn or Ala;

30 A10 is Tyr or D-Tyr;

A15 is Gly, Ala or D-Ala;

A22 is Leu, D-Leu, Lys or Ala; and

35 A30 is a bond or any amino acid sequence of 1 up to 15 residues and wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29.

32. The use as defined in claim 31, wherein said GHRH analogue or salt thereof is selected from the group consisting of, and wherein:

- A2 is D-Ala, A8 is Ala, A15 is Ala, A22 is Lys;
- A2 is D-Ala, A10 is D-Tyr, and A22 is Lys and;
- A2 is D-Ala, A10 is D-Tyr, A15 is D-Ala, and A22 is Lys.

33. The use as defined in claim 32, wherein A2 is D-Ala, A8 is Asn, A10 is D-Tyr, A15 is D-Ala, A22 is Lys and A30 is a bond.

34. The use according to claim 31, wherein said mammal has a disorder selected from the group consisting of hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union bone-fracture, acute/chronic debilitating illness or infection, wound healing, reduction of the incidence of post-surgical problems, lactation failure, infertility in women, cachexia in cancer patients, anabolic and/or catabolic problems, T-cell immunodeficiencies, neurodegenerative conditions, GHRH receptor-dependent tumors, aging, sleep disorders, muscle wasting diseases such as in sarcopenic patients, frail elderlies, HIV patients and cancer patients having radiotherapy and chemotherapy side-effects.

35. The use according to claim 34, wherein said muscle wasting diseases are selected from the group consisting of; sarcopenia, frailty in elderlies, HIV and cancer.

36. The use of a GHRH analogue, or a pharmaceutically acceptable salt thereof for stimulating secretion or synthesis of growth hormone in a mammal in need thereof, said GHRH analog or pharmaceutically acceptable salt comprising formula X: Tyr-A2-Asp-Ala-Ile-Phe-Thr-A8-Ser-A10-Arg-Lys-Val-Leu-A15-Gln-Leu-Ser-Ala-Arg-Lys-A22-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH<sub>2</sub>, wherein

A2 is Ala or D-Ala;

A8 is Asn, D-Asn or Ala;

A10 is Tyr or D-Tyr;

A15 is Gly, Ala or D-Ala;

A22 is Leu, D-Leu, Lys or Ala; and

A30 is a bond or any amino acid sequence of 1 up to 15 residues and

wherein said analogue comprises at least one amino acid substitution in the native form of hGHRH1-29.

37. The use according to claim 36, wherein said mammal has a disorder selected from the group consisting of hypothalamic pituitary dwarfism, burns, osteoporosis, renal failure, non-union bone-fracture, acute/chronic debilitating illness or infection, wound healing, reduction of the incidence of post-surgical problems, lactation failure, infertility in women, cachexia in cancer patients, anabolic and/or catabolic problems, T-cell immunodeficiencies, neurodegenerative conditions, GHRH receptor-dependent tumors, aging, sleep disorders, muscle wasting diseases such as in sarcopenic patients, frail elderlies, HIV patients and cancer patients having radiotherapy and chemotherapy side-effects.

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38. The use according to claim 37, wherein said muscle wasting diseases are selected from the group consisting of; sarcopenia, frailty in elderlies, HIV and cancer.